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Napsin A and Thyroid Transcription Factor-1-Positive Cerebellar Tumor with Epidermal Growth Factor Receptor Mutation

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Key Words
Cerebral metastases · Lung adenocarcinoma · Epidermal growth factor receptor mutation

Abstract
We present a very rare case of cerebellar metastasis of unknown origin, in which a primary lung adenocarcinoma was diagnosed by pathological examination of a cerebellar metastatic tumor, using immunohistochemical markers and epidermal growth factor receptor (EGFR) mutation of primary lung cancer. A 69-year-old woman was admitted to our hospital because of a hemorrhagic cerebellar tumor and multiple small brain tumors. She underwent cerebellar tumor resection. On pathological examination, the tumor was diagnosed as adenocarcinoma. However, the primary tumor site was unidentifiable even with several imaging inspections. On immunohistochemical analysis, the resected tumor was positive for napsin A and thyroid transcription factor-1. In addition, an EGFR mutation was detected in the tumor. Therefore, primary lung cancer was diagnosed and the patient was started on gefitinib (250 mg/day) therapy.

Introduction

Cerebral metastases of unknown origin are most frequently reported in association with primary lung cancer [1]. However, we could not find any reports in the literature in which the primary site was not detected within the lung fields.

The prognosis of cancer of unknown origin is poor, with median survival times of 6–12 months, and the advantage of chemotherapy over best supportive care remains unclear [2]. We present a very unique case of cerebellar metastasis of unknown origin,

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in which primary lung adenocarcinoma was diagnosed by pathological examination of the cerebellar metastatic tumor. Moreover, the tumor was successfully treated with gefitinib.

Case Presentation

A 69-year-old woman was admitted to our hospital because of dizziness. Brain CT and MRI revealed a cerebellar tumor with hemorrhage, as well as multiple small brain tumors (**fig. 1**a, b). The cerebellar tumor was resected because of the hemorrhage, while the other tumors were treated using Gamma-Knife radiosurgery. Adenocarcinoma was strongly suspected on pathological examination (**fig. 2**a); however, the primary tumor site was unidentifiable. Serum carcinoembryonic antigen (CEA) and sialyl Lewis X antigen (SLX) levels were 129.9 ng/ml and 150 U/ml, respectively. Other tumor markers were within the reference range. Malignancy was not detected in the mammary glands, or in gynecological or gastroenterological areas. Chest CT revealed enlarged submandibular (only the right side), infraclavicular, and subcarinal lymph nodes (**fig. 3**a–c). Fluorodeoxyglucose (FDG) positron emission tomography revealed high FDG uptake in these lymph nodes (maximal standardized uptake values of 3.8, 8.2, and 10.2, respectively; fig. 3g). The resected tumor was positive for napsin A and thyroid transcription factor-1 (TTF-1) (fig. 2b); an epidermal growth factor receptor (EGFR) exon 19 deletion mutation was also detected. These findings led us to strongly suspect lung adenocarcinoma (cTxN3M1b, stage IV). Thus, gefitinib (250 mg/day) treatment was initiated.

On day 19 of the therapy, chest CT revealed 60% shrinkage in lymph node volume (fig. 3d–f), particularly in the subcarinal lymph nodes. On day 46, serum CEA and SLX levels were 11.6 ng/ml and 29 U/ml, respectively.

Discussion

We successfully diagnosed a very rare case of lung adenocarcinoma with associated cerebellar metastasis of an unidentifiable primary site. Moreover, the patient immediately responded to gefitinib therapy.

Napsin A and TTF-1 are useful immunohistochemical markers for primary lung cancer in cases where the primary site is unknown [3]. TTF-1 and napsin A typically stain positive in cases of lung and thyroid cancers [3] and renal cell carcinoma, respectively [4]. However, the use of napsin A and TTF-1 together is reportedly more beneficial in diagnosing primary lung adenocarcinoma [5]; hence, we arrived at a diagnosis of lung adenocarcinoma although the primary site was initially unknown. EGFR mutation is a specific genetic mutation of lung cancer [6]. We were thus convinced that the primary tumor site was the lung.

Our case is unique because the cerebellar tumor was EGFR mutation positive, prompting the initiation of gefitinib therapy. Because gefitinib is effective in treating brain metastases of lung cancer with EGFR mutation [7], brain metastases may have been controlled in this case. The volumes of target lesions were reduced. This case may offer some useful insights concerning treatment of cerebral metastases of unknown origin.

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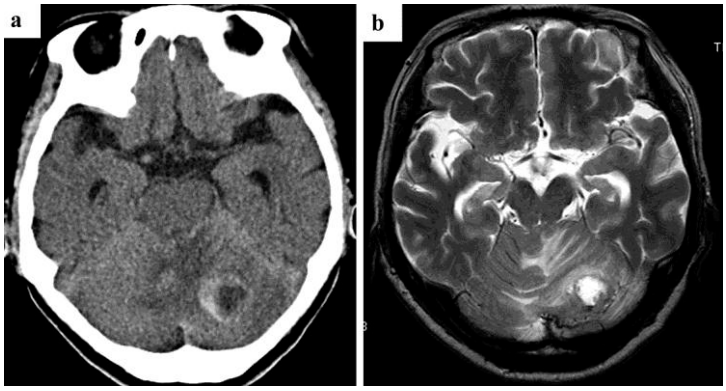

Fig. 1. a Brain CT showing cerebral tumor with hemorrhage. **b** T_2-weighted MRI image of the brain.

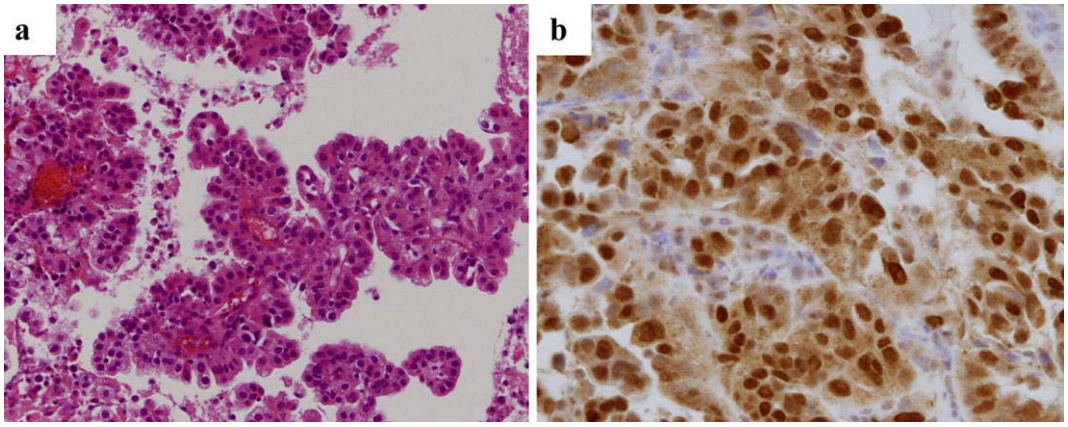

Fig. 2. Microscopic appearance of the cerebellar tumor specimen. **a** Tumor cells showing papillary and ductal arrangement (H&E staining). **b** Tumor cell nuclei and cytoplasm stained with adenocarcinoma cocktail antibodies comprising TTF-1 and napsin A antibodies.

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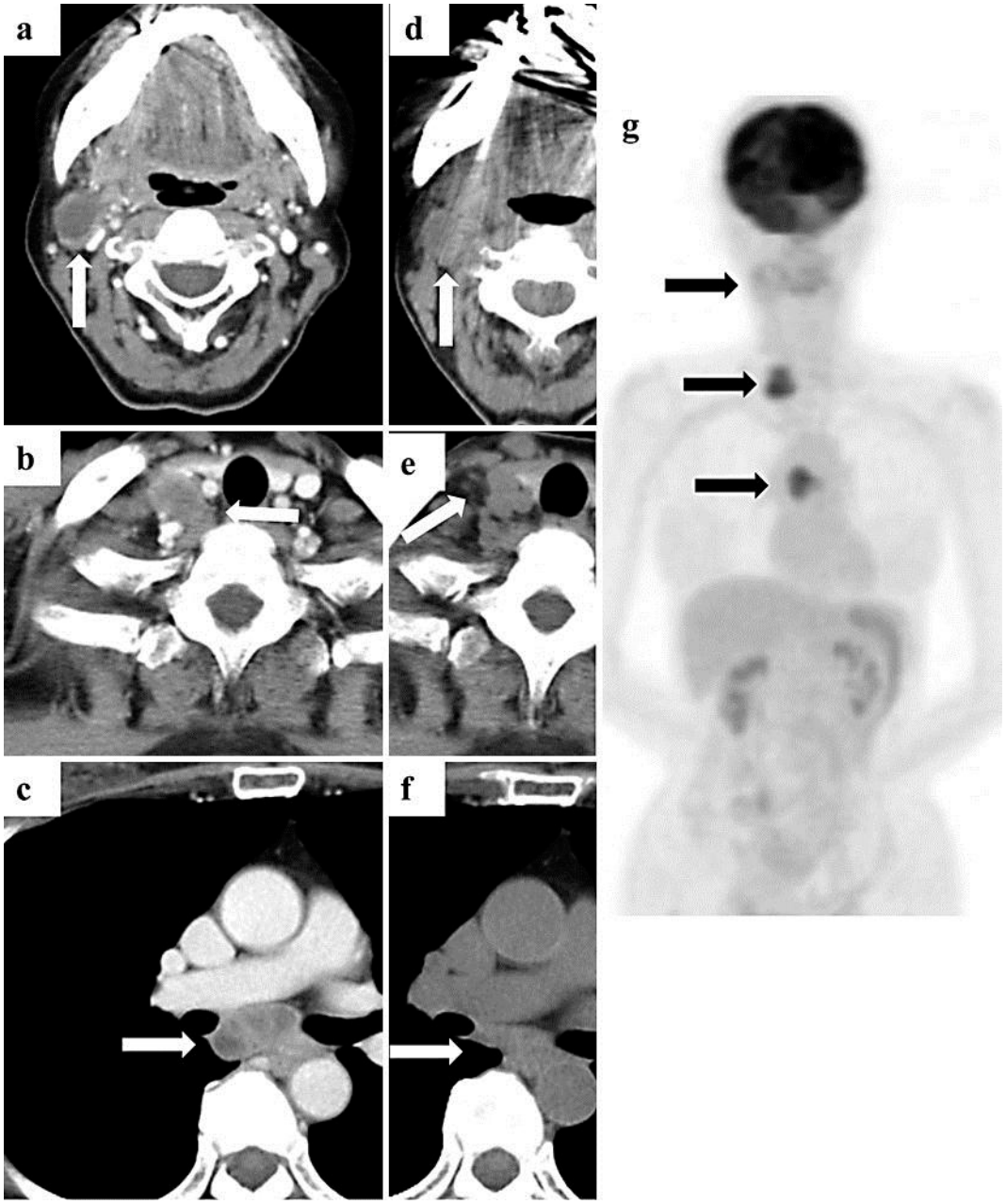

Fig. 3. Chest CT on admission (**a–c**) and on day 19 (**d–f**) of the chemotherapy course. **a**, **d** Right submandibular lymph node (arrows). **b**, **e** Right infraclavicular lymph node (arrows). **c**, **f** Subcarinal lymph node (arrows). **g** FDG positron emission tomography highlighting the above-mentioned lymph nodes (arrows) on admission.

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